1083-8791/07/1307-0001$32.00/0
doi:10.1016/j.bbmt.2007.03.011

ASBMT
American Society for Blood and Marrow Transplantation

Reduced-Intensity Conditioning for Unrelated Donor Progenitor Cell Transplantation: Long-Term Follow-Up of the First 285 Reported to the National Marrow Donor Program

Sergio Giralt, Brent Logan, Douglas Rizzo, Mei-Jie Zhang, Karen Ballen, Christos Emmanouilides, Rajneesh Nath, Pablo Parker, David Porter, Brenda Sandmaier, Edmund K. Waller, Juliet Barker, Steven Pavletic, Daniel Weisdorf

The Nonmyeloablative Study Group, Center for International Blood and Marrow Transplant Research and the National Marrow Donor Program, Minneapolis, Minneapolis

Correspondence and reprint requests: Sergio Giralt, MD, University of Texas M.D. Anderson Cancer Center, Blood and Marrow Transplant Program, 1515 Holcombe Boulevard, Houston, TX 77030 (e-mail: sgiralt@mdanderson.org).

Received February 15, 2007; accepted March 25, 2007

ABSTRACT

To determine the long-term outcome of patients undergoing unrelated donor transplantation (URD) after a reduced intensity conditioning (RIC) regimen, we performed a retrospective analysis of the transplant outcomes of the first 5 years of RIC experience as reported to the National Marrow Donor Program (NMDP). Patients were included if they were older than 18 years and had undergone a URD transplant procured through the NMDP from January 1, 1996 until May 31, 2001, with an RIC regimen for a hematologic malignancy. The number of URDs performed using an RIC increased from 59 during 1996 to 1999, to 149 in the year 2000. RIC recipients were older (53 vs. 33 years) and had a higher likelihood of having advanced disease (81% vs. 51%) when compared to patients undergoing a myeloablative conditioning regimen during the same time period. The 5-year survival rate is 23% (95% confidence interval [CI]; 18, 28), whereas the 5 year incidence of progression/relapse is 43.4% (95% CI; 37,49). Prognostic factors for better overall survival on multivariate analysis were earlier disease stage, longer time to transplant from diagnosis, better HLA match, ≥90% performance score, and use of peripheral blood stem cells. This analysis demonstrates that long-term survival and disease control can be obtained with URD progenitor cell transplantation after RIC conditioning. However, only prospective trials will define the optimal role of this therapy in patients with hematologic malignancies. Therefore, URD transplantation with RIC should continue to be explored in the context of clinical trials.

KEY WORDS

Unrelated donor stem cell transplantation • Long-term outcomes • Reduced-intensity conditioning regimens

INTRODUCTION

Unrelated donor (URD) cells represent the most common alternative source of hematopoietic stem cells for patients with hematologic malignancies who do not have an HLA compatible donor within the family [1]. High-dose chemoradiotherapy followed by infusion of URD stem cells can provide long-term disease control for a significant fraction of patients with a variety of malignant and nonmalignant disorders. However, this procedure is also associated with a significant risk of morbidity and mortality primarily because of graft-versus-host disease (GVHD) and infectious complications [1,2].

The most important risk factors for transplant-related morbidity and mortality after conventional URD transplantation are degree of HLA matching, disease status at the time of transplant, patient and donor age, as well as pre transplant performance status [1-4]. Non-relapse mortality (NRM) rates of over

50% are commonly reported in patients over the age of 40; thus, many centers are restricting the use of unrelated hematopoietic cell transplantation to younger patients with good performance status and minimal comorbidities. However, older and debilitated patients represent a large fraction of the patients with hematologic malignancies who could potentially benefit from an allograft through a graft-versus-malignancy effect or the recovery of a functioning bone marrow.

In an effort to reduce NRM in older and medically debilitated patients many investigators have explored the concept of reduced-intensity conditioning (RIC) regimens [5-9]. The rationale for this approach lies in the hypothesis that less intense preparative regimens will result in less recipient tissue damage and less release of inflammatory cytokines resulting in fewer toxicities and a lower incidence of GVHD [10,11].

The feasibility and efficacy of RIC regimens has been documented in multiple studies, mostly using matched sibling donors [5-9,12]. Recently, single and multi-institution reports demonstrating the feasibility of RIC regimens using unrelated and mismatched donors have also been reported [6,12-14]. We performed a retrospective analysis of transplant outcomes in patients receiving an RIC regimen as reported to the National Marrow Donor Program (NMDP) to describe the long-term outcomes of patients treated with an RIC regimen followed by URD progenitor cell transplantation, and to define potential prognostic factors for outcome.

PATIENTS AND METHODS

The National Marrow Donor Program

The NMDP was established in 1986 by an act of United States Congress, and is currently under contract with the Health Resources and Services Administration. The policies and procedures of the NMDP have been previously described [15]. The NMDP not only facilitates the search and procurement of unrelated donor progenitor cells and cord blood units, but also maintains a prospective database of transplanted patients that includes pretransplant demographics, disease specific variables, as well as posttransplant outcomes. In July 2004, the NMDP partnered with the Medical College of Wisconsin's International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry to form the Center for International Blood and Marrow Transplant Research (CIBMTR). The NMDP conducts its research program through the CIBMTR.

Patient Eligibility

To qualify for the analysis patients had to meet the following criteria: (1) undergone URD transplant from 1/96 to 05/01; (2) had a malignant disorder as defined by the NMDP recipient baseline and transplant data form; (3) 18 years or older at the time of the transplant; (4) received a conditioning regimen fulfilling 1 of the following criteria: (a) 500 cGy or less of total body irradiation (TBI); (b) 9 mg/kg or less of total busulfan dose; (c) 140 mg/m^2 or less total melphalan dose; (d) regimen included a purine analog either fludarabine, cladribine, or pentostatin.

These regimens all fulfilled the criteria used to define an RIC regimen as suggested by Champlin et al. [16-19], which include reversible myelosuppression within 28 days if given without stem cell support, mixed chimerism in a significant proportion of patients after allogeneic transplantation and limited extramedullary toxicity. Using these criteria, a total of 285 patients were available for analysis. Univariate and multivariate analyses of pre- and peritransplant variables was performed for the following transplant outcomes: acute and chronic GVHD (aGVHD and cGVHD), NRM, and overall survival.

Data Collection Methods

Data from each transplant center were collected prospectively on standardized forms. The NMDP validated the data for consistency and accuracy. All patients and donors were treated under local institutional review board (IRB) guidelines and provided written informed consent for treatment. Procedures for donor and recipient data submission to the NMDP were reviewed and approved by the NMDP IRB. All surviving recipients included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent was waived by the NMDP IRB for all deceased recipients. To address bias introduced by inclusion of only a proportion of surviving patients (those who consented) but all deceased recipients, a sample of deceased patients was selected using a weighted randomized scheme that adjusts for overrepresentation of deceased patients in the consented cohort.

Transplantation was done by the centers using their local protocols for conditioning regimen and GVHD prophylaxis. HLA matching for hematopoietic stem cell transplantation was based on antigen or allele identity between donor and recipient. Strategies for selecting a partially HLA-mismatched donor varied when a fully matched donor could not be identified. Selection of the RIC regimen for transplantation was at the discretion of the transplant center, and the rationale for this selection was not collected by the NMDP.

Univariate Analysis and Multivariate Analysis

Nonrelapse mortality was defined as death from any cause other than relapse. aGVHD and cGVHD were scored according to standard published criteria

[20,21]. Overall survival (OS) rates were calculated by the methods of Kaplan and Meier, and comparisons between groups were made using the log-rank statistics [22,23]. Probabilities of aGVHD and cGVHD, NRM, and relapse were calculated using cumulative incidence estimates to accommodate competing risks [24].

Cox proportional hazards regression was used to fit a multivariate model for OS. Factors considered for a model were HLA match, year of transplant, source of stem cells, diagnosis, donor/recipient CMV status, disease status prior to transplant, recipient age, use of antithymocyte globulin (ATG/ALG), Karnofsky performance score prior to transplant, ABO compatibility, prior transplant, and donor/recipient sex match. Risk factors were included in the final model only if the Wald chi-square statistic yielded a P-value = .05 [25]. The assumption of proportional hazards for each covariate was tested using time-dependent covariates. Possible interactions between factors were investigated, but none were significant at a P-value $\leq$.01.

Chimerism

A variety of methods were used to determine chimerism as reported by the transplant centers to the NMDP including conventional cytogenetics, restriction fragment length polymorphisms, and polymerase chain reaction [26]. The results of the first chimerism analysis (usually performed between 1 and 3 months posttransplant) are reported.

RESULTS

Patient and Treatment Characteristics

Patient and treatment characteristics are summarized in Table 1. In brief, median age was 53 years (range: 18-79). Sixty-four percent of the recipients were male. Non-Hodgkin's lymphoma was the most common indication for URD transplantation with RIC followed by acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML). The median time from diagnosis to transplant was 23 months (range: 0.7-308). The conditioning regimen most commonly included fludarabine in combination with TBI (30%), busulfan (23%), melphalan (20%), or cyclophosphamide (16%). GVHD prophylaxis consisted of either cyclosporine or tacrolimus in combination with other agents. ATG or ALG was administered to 31% of the recipients. The regimens and GVHD prophylaxis used stratified by diagnosis are summarized in Table 2.

Characteristics of Reduced Intensity Conditioning Recipients Compared to Conventional Allografts

When compared to patients undergoing an URD transplant using a conventional myeloablative conditioning regimen during the same time period, recipients of RIC were older (median age: 53 vs. 33) and had a higher likelihood of having Hodgkin's Disease, non-Hodgkin lymphoma, or a Plasma Cell disorder (39% vs. 8%). These patients also had a higher likelihood of having advanced disease (81% vs. 51%) and receive peripheral blood stem cells (PBSC) rather than bone marrow (46% vs. 5%). Table 3 summarizes the differences between recipients of RIC and the patients who underwent an ablative URD transplant during the same years.

Outcomes

Chimerism data between 1 and 3 months posttransplant were available for 234 patients. The median percentage of donor cells was 84% (range: 0-100). A total of 21 (11%) patients never had any evidence of donor cell engraftment (i.e., primary graft failure).

The cumulative incidence of grade II-IV aGVHD for the whole group was 39% (95% confidence interval [CI]; 33;45), the cumulative incidence of grade III-IV aGVHD was 22% (95%CI 17;27). The cumulative incidence of cGVHD at 2 years was 41% (95% CI; 35;46). The NRM rate at 3 months was 19% (95% CI: 15;24). Currently 66 patients are alive at a median of 61 months (range: 13-87 months). The 5 year OS rate is 23% (95% CI: 18,28). A total of 125 patients have relapsed or progressed, the relapse rate at 5 years for the whole group was 43% (95% CI: 37,49).

Because of the high degree of the patients, disease, disease state, and treatment heterogeneity, multivariate analysis was performed only for OS. Multiple variables were considered for the multivariate analysis, among them recipient age, disease stage, performance status, year of transplant, time from diagnosis to transplant, HLA matching, donor-recipient cytomegalovirus (CMV) status, donor-recipient sex match, stem cell source, and whether the URD transplant was a first or second transplant. Conditioning regimens, GVHD prophylaxis, and the source of stem cells are generally considered together as a "package" for hematopoietic transplantation at most centers. As such, their effects on transplant outcome cannot be considered independently. Table 4 summarizes transplant outcome. Table 5 summarizes those factors significantly associated with increased risk of death include use of bone marrow as the source of stem cells, intermediate or advanced disease at transplant, Karnofsky performance score <90, HLA mismatch between donor and recipient, and time from diagnosis to transplant shorter than 12 months.

DISCUSSION

It has now been 10 years since the first trials of RIC regimens for allogeneic transplantation in pa-

Table 1. *Characteristics of Patients Receiving URD Cell Transplants Using Reduced Intensity Conditioning Regimens*

Variable	N Eval.	N	%
Recipient sex	285		
Female		102	(36)
Male		183	(64)
Recipient age in years	285		
Recipient age median (range)		53 (18-79)	
<40		54	(19)
40 to 50		61	(21)
>50		170	(59)
Diagnosis and diseases stage	285		
Acute lymphocytic leukemia		9	(4)
CR1/CR2		2/2	(2)
>CR2		3	(1)
Not in remission		2	(1)
Acute myelogenous leukemia		60	(21)
CR1/CR2		22/14	(12)
>CR2		3	(1)
Not in remission		21	(8)
Chronic myelogenous leukemia		43	(15)
First chronic phase		12	(4)
Advanced CML/myeloproliferative disease (MPD)		31	(11)
Chronic lymphocytic leukemia		30	(10)
Hodgkin's lymphoma		16	(6)
Non-Hodgkin's lymphoma		65	(22)
Myelodysplastic syndromes		28	(10)
Plasma cell disorders		34	(11)
Performance status prior to transplant (Karnofsky)	285		
90-100		167	(59)
<90		99	(35)
Missing		19	(7)
Time from diagnosis to transplant in months	285		
Median (range)		23 (0.7-308)	
0-12		62	(22)
12-36		117	(41)
≥36		101	(35)
Missing		5	(2)
Donor age in years	285		
Median (range)		37 (19-59)	
Donor/recipient sex match	285		
Female donor-female recipient		55	(19)
Female donor-male recipient		43	(15)
Male donor-female recipient		47	(16)
Male donor-male recipient		140	(49)
HLA match (intermediate resolution for -A, -B, and high resolution for -DRB1)	285		
Match		248	(87)
Mismatch		37	(13)
Donor/recipient CMV status	285		
Donor negative/recipient negative		70	(24)
Donor negative/recipient positive		98	(34)
Donor positive/recipient negative		39	(14)
Donor positive/recipient positive		62	(22)
Unknown		16	(6)
Donor/recipient blood group match	285		
Match		116	(41)
Mismatch		167	(58)
Missing		2	(1)
Conditioning regimen	285		
Fludarabine + ≤500 cGy TBI ± other		86	(30)
Fludarabine + cyclophosphamide ± other		46	(16)
Fludarabine + melphalan ≤ 140 mg/m² ± other		57	(20)
Fludarabine + busulfan ≤ 9 mg/kg ± other		66	(23)
Fludarabine + cytarabine ± other		20	(7)
Other		10	(4)
Source of stem cells	285		
PBSC		131	(46)
Bone marrow		154	(54)
GVHD prophylaxis	285		
Cyclosporine based		151	(54)
Cyclosporine + mycophenolate mofetil ± other		107	(38)
Cyclosporine + methotrexate ± other		7	(2)
Cyclosporine + other		37	(13)
Tacrolimus based		130	(45)
Tacrolimus + mycophenolate mofetil ± other		12	(4)
Tacrolimus + methotrexate ± other		100	(35)
Tacrolimus + other		18	(6)
Other		4	(1)
ATG/ALG prior to transplant	285		
Yes		88	(31)
No		197	(69)
First transplant	285		
Yes		186	(63)
No		99	(37)

HLA indicates human leukocyte antigen; CMV, cytomegalovirus; TBI, total body irradiation; PBSC, peripheral blood stem cells; GVHD, graft-versus-host disease; ATG, antithymocyte globulin; ALG, antilymphocyte globulin.

tients with hematologic malignancies were described. RIC regimens can exploit a graft versus tumor effect in conjunction with limited peritransplant morbidity [6-9,11-14]. Data from the IBMTR and the EBMT have shown a dramatic increase in the number of allografts that are being performed using RIC regimens [27,28]. Although the definition of an RIC regimen is imprecise, these regimens typically involve agents that are used in the setting of standard myeloablative regimens at lower doses, and at least for cyclophosphamide, melphalan, and TBI have been shown to be associated with reversible myelosuppression [16-19]. The definition of RIC used in this analysis has been broadly used by the CIBMTR and the NMDP in performing other retrospective analyses.

In this analysis we describe the long-term outcomes of patients who underwent a URD transplant after an RIC regimen during the first 5 years of use of this treatment modality. Our main objective was to determine whether long-term survival and disease control was feasible, and because of the cohort heterogeneity we did not attempt to analyze the efficacy of RIC for any specific indication.

Table 2. *Distribution of Diagnosis and GVHD Prophylaxis by Conditioning Regimen*

	Total	Flu/AraC	Flu/Bus	Flu/Cyc	Flu/Mel	Flu/TBI	Others
Diagnosis							
ALL, AML, MDS	97	1	27	9	22	34	4
CML and MPD	43	1	11	6	7	18	0
CLL, lymphoma	111	18	19	29	16	23	6
PCD	34	0	9	2	12	11	0
Total	285	20	66	46	57	86	10
GVHD Prophylaxis							
CSA based	151						
CSA-MMF	107	0	8	15	5	71	8
CSA-MTX	7	1	3	1	2	0	0
CSA-other	37	1	12	12	8	4	0
Tacro based	134						
Tacro-MMF	12	0	4	3	4	1	0
Tacro-MTX	100	16	28	15	37	3	1
Tacro-other	18	2	10	0	0	6	0
Other	4	0	1	0	1	1	1
Total	285	20	66	46	57	86	10

ALL indicates acute lymphocytic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndromes; CML, chronic myelogenous leukemia; MPD, myeloproliferative disorder; CLL, chronic lymphocytic leukemia; PCD, plasma cell disorders; GVHD, graft-versus-host disease; CSA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; Tacro, tacrolimus.

The observation that at 5 years posttransplant 23% of patients are alive and 18% are alive and free of progression or relapse demonstrates that long-term survival and disease control is feasible with this treatment strategy, despite the older age and that only 19% of patients underwent this treatment early in the course of their disease. This analysis was not intended to define the relative benefit of URD transplantation

Table 3. *Characteristics Of RIC Patients Compared To Conventional Myeloablative URD Allografts Over The Same Time Period*

	RIC Patient			Myeloablative		
Variable	**N Eval.**	**N**	**%**	**N Eval.**	**N**	**%**
Recipient sex	285			5653		
Female		102	(36)		2376	(42)
Male		183	(64)		3277	(58)
Recipient age in years	285			5653		
Recipient age median (range)		53 (18-79)			33 (0.2-67)	
<40		54	(19)		3719	(66)
40-50		61	(21)		1301	(23)
>50		170	(60)		633	(11)
Diagnosis	285			5653		
ALL		9	(4)		1206	(21)
AML		60	(21)		1486	(26)
CML		43	(15)		1778	(31)
Hodgkin's lymphoma		16	(6)		42	(1)
Non-Hodgkin's lymphoma		65	(22)		330	(6)
Myelodysplastic disorders		28	(10)		570	(10)
Plasma cell disorders		34	(11)		76	(1)
Other leukemia		30	(10)		165	(3)
Disease stage prior to transplant	285			5653		
CR1/CR2/CP1		54	(19)		2758	(49)
Other		231	(81)		2895	(51)
Performance status prior to transplant	285			5653		
90 or higher		167	(58)		3930	(70)
<90		99	(35)		1618	(29)
Missing		19	(7)		105	(2)
ATG/ALG prior to transplant	285			5653		
Yes		88	(31)		1193	(21)
No		197	(69)		4460	(79)
Source of stem cell	285			5653		
PBSC		131	(46)		284	(5)
Marrow		154	(54)		5369	(95)

Table 4. *Transplant Outcomes after RIC Conditioning*

Outcome	Estimate (95% CI)
Survival	
at 1 year	44.2% (38.8%-50.4%)
at 3 years	28.3% (23.5%-34.1%)
at 5 years	23.0% (18.5%-28.5%)
PFS	
at 1 year	30.9% (25.9%-36.7%)
at 3 years	22.2% (17.9%-27.7%)
at 5 years	18.0% (14.0%-23.2%)
NRM	
at 100 days	18.8% (14.5%-23.6%)
at 1 year	30.1% (24.9%-35.6%)
at 3 years	35.9% (30.3%-41.5%)
at 5 years	38.6% (32.9%-44.3%)
Relapse/progression	
at 1 year	39.0% (33.3%-44.7%)
at 3 years	41.9% (36.1%-47.6%)
at 5 years	43.4% (37.5%-49.1%)
Chronic GVHD	
at 1 year	38.6% (32.9%-44.3%)
at 3 years	40.8% (35.0%-46.5%)
at 5 years	40.8% (35.0%-46.5%)

PFS indicates progression free survival; NRM, Nonrelapse mortality; GVHD, graft-versus-host disease; CI, confidence interval.

with an RIC regimen over other conventional transplant and nontransplant approaches, but it should provide the basis for the design and implementation of controlled clinical trials aimed at defining the role of RIC in specific disease entities and stages [29-32].

Disease stage, performance status, stem cell source, HLA matching, and timing of transplant emerged as the most important prognostic factors for survival after RIC URD transplant, and should be considered when planning and designing future trials with this treatment modality. Patients with more advanced disease had a 77% increase risk of death when compared to patients transplanted early in the course of their disease. This increase in deaths was related primarily to increases in relapse risk but also in NRM rates. These data support continued exploration of this treatment modality in patients with hematologic malignancies early in the course of the disease, particularly in the absence of other effective therapies (i.e., MDS and acute leukemia). In other hematologic malignancies this treatment option needs to be explored in the context of new emerging nontransplant therapies.

We observed a potential advantage of PBSC over bone marrow that requires further study. Previously, an advantage for PBSC compared to bone marrow has only been demonstrated using low-dose TBI conditioning, where a higher risk of graft failure was observed using marrow grafts [32]. In this larger analysis, the use of PBSC was associated with superior OS independent of conditioning regimen. This observation parallels the observations after sibling and unrelated donor transplantation in adults [33-38]. However, confirmatory data from prospective, randomized comparisons of peripheral blood versus bone marrow unrelated grafts are still lacking. An ongoing Blood and Marrow Transplant Clinical Trials Network study (BMT CTN 0201) may answer this important question.

Dose intensity has been the mainstay of conventional allografting, and single institutional studies have shown that myelogenous leukemia patients results fare better using more intense regimens, often including either melphalan or busulfan [39]. Variability in RIC regimens may yield different outcomes in specific diseases and disease stages. This retrospective analysis did not identify any disease or disease state in which 1 regimen was associated with superior outcomes. Therefore, carefully designed prospective trials in individual diseases are essential to determine the contribution of the specific conditioning regimen to effective disease control.

Table 5. *Factors Related to Risk of Death as Identified by Multivariate Analysis*

Variable	Level	N	RR (95%CI)	*P*-Value
Stem cell source	**BM**	**149**	**1.00**	
	PB	**124**	**0.65 (0.48-0.86)**	**.003**
Disease stage	**CR1/CP1/RA/RARS**	**36**	**1.00**	
	Intermediate/Advanced	**237**	**1.77 (1.09-2.86)**	**.020**
HLA matching	**Matched**	**239**	**1.00**	
	Mismatched	**34**	**1.51 (1.01-2.26)**	**.043**
Karnofsky Score	**≥90**	**159**	**1.00**	**.031[a]**
	<90	**98**	**1.49 (1.10-2.01)**	**.009**
	Missing	**16**	**1.08 (0.58-2.01)**	**.804**
Time from diagnosis to transplant				**<.001[a]**
	≤12 months	**62**	**1.00**	
	12 to 36 months	**117**	**0.60 (0.41-0.88)**	**.009**
	>36 months	**94**	**0.44 (0.29-0.67)**	**<.001**

RR indicates relative risk; CI, confidence interval; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; CR1, first complete remission; CP1, first chronic phase.

[a]Two degrees of freedom test.

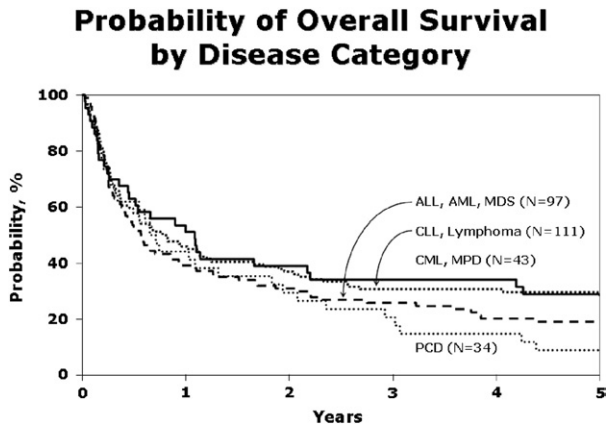

Figure 1. Overall survival by disease category after nonablative stem cell transplant.

As with conventional ablative transplantation the causes of treatment failure remain GVHD, infections, and disease recurrence. These, however, may be more difficult to control or have a more serious impact on the older and debilitated patients with comorbidities who are currently being treated with RIC transplants [40-42]. The data from these first 285 patients underscore the need for careful selection of patients and donors. Other large retrospective single and multi-institutional analysis has reported long-term outcome data of patients undergoing RIC unrelated donor transplantation. Among these, the Seattle Consortium recently reported the results of 122 patients undergoing allogeneic transplantation using fludarabine in combination with 200 cGy of TBI, OS at 2 years was reported as 48%; interestingly, in this study recipients of URD stem cells actually had a trend toward a better OS at 2 years (63% vs. 44%) than patients receiving cells from a matched related donor, because of a lower risk of relapse (16% vs. 50%) (45). Longer follow-up studies will be important to assess the durability of this apparent benefit.

In conclusion, URD transplantation after an RIC can result in long-term survival and disease control for a fraction of patients with hematologic malignancies. Patients with advanced disease at the time of transplant do poorly, and should be considered for RIC therapy only in the context of a clinical trial incorporating new agents or strategies aimed at improving long-term disease control. The role of RIC in individual diseases particularly in early stages requires well-controlled trials against alternative transplant as well as nontransplant strategies. According to our analysis, these studies should take into account the impact of disease stage, HLA matching, and stem cell source when designed and implemented (Table 5, Figure 1).

ACKNOWLEDGMENTS

The CIBMTR is supported by Public Health Service Grant U24-CA76518 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute; Office of Naval Research; Health Services Research Administration (DHHS); and grants from Abbott Laboratories; Aetna; American International Group, Inc.; American Red Cross; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; AnorMED, Inc.; Astellas Pharma US, Inc.; Baxter International, Inc.; Berlex Laboratories, Inc.; Biogen IDEC, Inc.; BloodCenter of Wisconsin; Blue Cross and Blue Shield Association; Bristol-Myers Squibb Company; BRT Laboratories, Inc.; Cangene Corporation; Celgene Corporation; CellGenix, Inc.; Cell Therapeutics, Inc.; CelMed Biosciences; Cylex Inc.; Cytonome, Inc.; CytoTherm; DOR BioPharma, Inc.; Dynal Biotech, an Invitrogen Company; Enzon Pharmaceuticals, Inc.; Gambro BCT, Inc.; Gamida Cell, Ltd.; Genzyme Corporation; Gift of Life Bone Marrow Foundation; GlaxoSmithKline, Inc.; Histogenetics, Inc.; HKS Medical Information Systems; Kirin Brewery Co., Ltd.; Merck & Company; The Medical College of Wisconsin; Millennium Pharmaceuticals, Inc.; Miller Pharmacal Group; Milliman USA, Inc.; Miltenyi Biotec, Inc.; MultiPlan, Inc.; National Marrow Donor Program; Nature Publishing Group; Novartis Pharmaceuticals, Inc.; Osiris Therapeutics, Inc.; Pall Medical; Pfizer, Inc.; Pharmion Corporation; PDL BioPharma, Inc; Roche Laboratories; Sanofi-aventis; Schering Plough Corporation; StemCyte, Inc.; StemSoft Software, Inc.; SuperGen, Inc.; Sysmex; The Marrow Foundation; THERAKOS, Inc.; University of Colorado Cord Blood Bank; ViaCell, Inc.; ViraCor Laboratories; Wellpoint, Inc.; and Zelos Therapeutics, Inc. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government. BS acknowledges grant support from CA18029 and CA78902.

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